Claim 20, line 1: Change "pharmaceutical composition" to -- kit --.

Claim 21, line 1: Change "pharmaceutical composition" to -- kit --.

22. (Amended) A [pharmaceutical composition] kit useful for the treatment of cancer comprising at least two containers, each comprising an [effective] amount of MHC molecules which may be found in an animal tissue, serum or cell source different from that of the other container which is effective to treat cancer.

24. (Amended) The method of claim 14, comprising administering to said patient [effective] amounts of at least two doses of MHC molecules, one extracted from an animal tissue, serum or cell source and the other extracted from a different such source which are effective to treat cancer.

REMARKS

We note that the 1449 form of the IDS submitted on August 11, 1998 was initialed at the bottom as having been considered on 10/21/98, but none of the four references was individually initialed. It appears clear that all four references were considered.

Claims 10 and 17-22 have been amended to clarify that the "pharmaceutical composition" being claimed is in the form of a "kit."

It is clear from the disclosure at, *e.g.*, page 4, lines 14-17, that the two sources of animal tissue, serum or cells of, *e.g.*, claim 17, encompass any combination of MHC molecules taken from different species (or from different members of the same species - see p. 1, line 5, which discloses the use of alloantigens, which, according to Stedman's Medical Dictionary (attached), are antigens "that occur in some, but not all, members of the same species") or from different tissues, sera or cells of the same animal (including different batches of the same - see p. 4, line 16 and p. 7, line 4)." Therefore, the claim language is clear.

An "effective amount" of MHC molecules, as recited, *e.g.*, in claims 14, 17, 22 and 24, clearly refers to an amount which is effective to treat cancer, as is now made even more clear in the claims.

The rejections under **35 U.S.C. 112, first paragraph** fall into three legally relevant categories of allegations: 1) that the disclosed rat model is allegedly not an art-recognized one for cancer; 2) that the specification allegedly does not teach how to make the claimed composition; and 3) that the specification allegedly does not teach how to use the claimed composition.

1) The **model** is, in fact, a well-established, art-recognized one for cancer generally.

Attached, for example, is a paper by Ferrero *et al* (1995. *Int. J. Immunotherapy* XI (2), 57-63) which, using the identical model of pleural tumors in rats, describes local regional immunotherapy by agents such as IL-2 and LAK cells. Like the rats of the instant application, the rats of the attached publication were inoculated in their lungs with Yoshida AH-130 ascites hepatoma cells. The authors confirm that the inhibition of tumor cell growth in this model is correlated with the decrease of other cancer symptoms, such as impaired respiratory function and, most importantly, death. Note that the authors extrapolate the value of the model beyond the specific case which they describe: they emphasize that the model can also be used to study localized immunotherapy of other types of tumors, such as mesotheliomas (see, *e.g.*, Discussion, first sentence of the second paragraph) and to study other immunotherapeutic treatments (see, *e.g.*, Abstract). Under longstanding case law, where models are disclosed and established as reasonably correlated with end uses, they can be used to provide proof of efficacy and, correspondingly, guidance (supplemental, here) of how to use an invention (*Cross v. Iizuka*, 224 USPQ 739 (CAFC 1985)).

The specific factors alleged by the Examiner to suggest that the model is allegedly inappropriate for the study of cancer do not support such a conclusion: a) It is irrelevant whether the model is only useful for a treatment method in which a therapeutic agent is administered directly to the site of tumor inoculation. Applicant has also shown that systemic administration (*e.g.*, the intraperitoneal and subcutaneous routes of administration exemplified in Example B at p. 8 of the specification) is effective. In any event, as discussed above, the model is used by skilled workers to draw conclusions beyond the specific conditions stated. b) It is incorrect that the model as used in the specification fails to reflect the growth rate of tumors or that the timing of treatment in the model is inconsistent with the treatment of cancers. The number of cells inoculated into the rats (approximately 250,000 cells) was selected to simulate an already partially developed cancer; by treating the rats at various times after inoculation of the tumor tissue, an investigator can study the treatment of tumor cells at various stages of growth. c) It is incorrect that the model as used by applicant is limited only to the treatment of immunosuppressed animals. Nude rats are used in only one experiment (shown in Fig. 6). d.) It is incorrect that the rats do not exhibit increased survival rates post treatment. The fact is that the survival time of rats has been shown to increase up to 29 ± 5 days (mean ± SEM of 8 experiments) following the suspension of administration according to the invention. The data are not being presented in the form of a Declaration because they are not necessary for allowance. As established herein, no "reasons or evidence" have been provided to doubt the

accuracy of the specification's assertions and its test results showing that the invention works as disclosed. See *In re Langer*, 183 USPQ 288 (CCPA, 1974) and MPEP 2164.07.

With regard to other objections raised by the Examiner concerning the model: a) The allegation that the model is "at best an alternate to an in vitro culture" is both incorrect and irrelevant. The model is, in fact, an art-recognized *in vivo* model for cancer, as is discussed above. Furthermore, even if the exemplified model had been an *in vitro* one, case law holds that an *in vitro* model suffices for patent purposes, provided that it is an art accepted one that exhibits a reasonable correlation with the disease in question (*Cross v. Iizuka*, 224 USPQ 739 (CAFC 1985); *In re Brana*, 34 USPQ2d 1426 (CAFC 1995); MPEP 2164.04). b) In any event, it is not necessary for Applicant to provide working examples "of an effective treatment of cancer," as required by the Examiner, particularly in view of the fact that the disclosed model is an art-accepted one that exhibits a reasonable correlation with the disease in question (*Nelson v. Bowler*, 206 USPQ 881; MPEP 2164.02).

2) The specification does, in fact, teach **how to make** the claimed composition.

It is incorrect that, as alleged by the Examiner, the disclosed composition contains components other than MHC molecules which could themselves have therapeutic benefits. The detergent extraction methods disclosed, *e.g.*, in Example II, are well-known in the art to selectively extract MHC molecules. See, *e.g.*, specification, p. 3, second paragraph; and Labeta *et al* (1988). *Journal of Immunological Methods* 112, 133-138, cited in the search report of the PCT and of record herein. Such an extract is demonstrated to be effective. See, *e.g.*, Figure 5.

3) The specification does, in fact, teach **how to use** the claimed composition.

As a preliminary comment, there is a distinction between "utility" under 35 U.S.C. 101 and the "how to use" requirement of 35 USC 112, paragraph 1. A demonstration of the utility of an invention can be satisfied by a showing that the inventive method "works," *e.g.*, in an art-recognized disease model. As was discussed in section 1) above, the model disclosed in the instant specification is an art-recognized one which exhibits a reasonable correlation with cancer. In order to satisfy the "how to use" enablement requirement of 35 USC 112, first paragraph, applicant need merely disclose sufficient information that a skilled worker can carry out the inventive method without undue experimentation. Often, this requires nothing more than disclosing the identity of new compositions, skilled workers being able routinely to determine suitable use details.

In this case, the specification clearly provides more than required to satisfy that

requirement. For example, the specification teaches an appropriate treatment regimen. (See, *e.g.*, page 6, line 24 to page 7, line 11). Moreover, the information and data provided in the specification, *e.g.*, showing results using the art-recognized model further guide skilled workers who are familiar with its interpretation. Experiments disclosed in the instant application, for example, involve systemic administration. Moreover, the attached paper by Ferrero *et al* shows model results involving treatment using IL-2 which are similar to those of the claimed composition when evaluated in the very same assay. Of course, IL-2 is known to be a general antineoplastic agent against a broad spectrum of tumors (see attached copy of a page from the Merck Index). This buttresses the credibility of the specification's disclosure regarding the general applicability of the claimed composition.

Furthermore, the specification clearly teaches a treatment regimen for humans (see, *e.g.*, the final paragraph at p. 6 of the specification). A disclosure of the specific dosages to be administered is not required in order to establish enablement *(Cross v. Iizuka et al*, 224 USPQ 739 (CAFC 1985); *In re Bundy*, 209 USPQ 48 (CCPA 1981); MPEP 2164.01 (c), second paragraph).

In view of these comments, withdrawal of the rejection is respectfully requested.

Respectfully submitted,

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